From: Subramaniam, Ravi [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP
(FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=E738F9D27062486E9047184B867FD968-SUBRAMANIAM, RAVI]
Sent: 4/15/2014 12:03:02 AM
To: Kenny Crump [KennyCrump@email.com]
Subject: RE: workshop

By "generally" I mean that typically the dose-response functions used in modeling tox data are concave upwards at dose levels of interest for environmental exposures. In those cases, . . .

I do not understand why one needs to necessarily posit a *threshold* (although one could) at endogenous levels to make the argument made in the indented portion of the text in my email of April 7 below. In the figure in slide 6 of your presentation, the curve can be low dose linear but curve upwards, as it does, below C0.

The tone is fine. Discuss more tomorrow.

Regards,
Ravi.

Ravi Subramaniam, PhD; Associate, Quantitative Methods Branch, IRIS Division, NCEA-ORD, US EPA
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From: Kenny Crump [mailto:KennyCrump@email.com]
Sent: Tuesday, April 08, 2014 10:29 AM
To: Subramaniam, Ravi
Subject: [SPAM] RE: workshop

Thanks, Ravi.

I'll take you suggestions under consideration. I am not sure about "slope assumed by bottom-up approach is generally a LOWER bound on the actual slope" What do you mean by "generally"? I can certainly think of situations (e.g., dose responses) where it would not be less than the actual slope.

I think your argument for concave upward makes good sense, but is there some way to suggest a threshold at some endogenous level. E.g., have arguments been made that I could refer to that suggest a threshold that might apply to endogenous levels?

Any suggestions about tone? I don't want to turn people off.

I will be getting in late Sunday night. However, if you want to get together, Tuesday is a possibility.

Regards,

Kenny

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From: Subramaniam, Ravi [mailto:Subramaniam.Ravi@epa.gov]
Sent: Monday, April 07, 2014 2:51 PM
To: Kenny Crump
Subject: RE: workshop

Hi Kenny,

Good to hear that you accepted the invite. Yes, the fundamental issue is pretty simple, isn't it? We have essentially made the same points to Tom in previous conversations. Because they have presented at various occasions, have been provided a lot of publicity by the Alliance for Risk Assessment, and have published this twice, the approach has gathered *de facto* credibility. A reason that people buy into this is because of "optical" reasons--it is being presented as conservative on account of adopting a linear approach.

On the header on slide 6: The point they make is not that they have the correct slope but that it is a conservative upper bound. You could change your header to "slope assumed by bottom-up approach is generally a LOWER bound on the actual slope".

Although not *needed* to illustrate the flaw, it may be useful to add a biological argument in defense of the sublinear curve you have drawn with the change in curvature occurring below the endogenous concentration. How about an abbreviated version of:

> Although not necessary to illustrate the flaw in the upper bound argument in Starr et al, one can think of reasons for a dose-response with concave upward curvature (as drawn). Endogenous defensive mechanisms are likely to become less effective in dealing with endogenous adducts as their levels increase over the endogenous range. It is plausible that organisms would have evolved some level of defensive mechanisms to deal with endogenous levels of adducts. However, there is an energy cost associated with over-capacity; thus, these defensive capabilities are not fully effective over the entire endogenous range, and this is consistent with the observance of "background" rates of cancer.

I will provide more specific comments if any by Friday. Things are quite busy here with multiple chemicals, Cr6 being one of them, and I am on leave tomorrow.

It would be nice to meet you. If you are coming in early enough on Sunday we can meet Sunday evening; else on Tuesday.

Regards,
Ravi.

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From: Kenny Crump [mailto:KennyCrump@email.com]
Sent: Monday, April 07, 2014 2:38 PM

To: Subramaniam, Ravi
Subject: RE: workshop

Ravi,

Attached are my draft slides for the Formaldehyde Workshop. My draft comments are also included. Please don't share this with anyone else. I would like any thoughts you have to share regarding this material. I am trying to keep my talk very simple and focused on the "fatal flaw" in the bottom-up approach.

I have discussed the workshop with Tom Starr and we have agreed to share information before the workshop.

The agenda on the web so far seems very general, and I don't see any discussion planned of BBDR modeling. Do you expect any?

I tentatively plan to be at the RDC in Hyattsville next week starting on Monday but my plans may change. I have reservations Sunday-Thursday at the

Embassy Row
2015 Mass. Ave.
202-265-1500

It would be great to get together with you if we have chance.

Regards,

Kenny

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From: Subramaniam, Ravi [mailto:Subramaniam.Ravi@epa.gov]
Sent: Friday, March 21, 2014 7:13 AM
To: kennycrump@email.com
Subject: workshop

Hi Kenny:

I understand they are likely to postpone the formaldehyde workshop by a month although decision may not have yet been taken. Did the contractor straighten out the communication regarding your role with you?

Are you in Hyattsville, MD now? If so, it would be nice to meet.

Ravi.

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